

REMARKS

Upon entry of the above amendment, claims 1, 16, 17 and 18 will be pending, claims 11, 12 and 14 having been canceled and new claims 16-18 added. Support for the amendments and the new claims can be found in the specification and in the original claims. Support for new claim 16 can be found, for example, in original claim 11 and in the specification at page 9, line 26, page 12, lines 7-11 and in Example 3. Support for new claim 17 can be found, for example, in the specification at page 1, lines 21-24. Support for new claim 18 can be found, for example, in original claim 14 and in the specification at page 12, lines 7-11. No new matter has been added.

Applicant respectfully requests entry of the above amendment and allowance of the new claims in view of the remarks in this Response.

35 U.S.C. §101

The Examiner rejected claims 11, 12 and 14 for alleged lack of patentable utility. Without conceding that the claims as previously presented fail to satisfy this requirement, and solely for the purpose of furthering prosecution, claims 11, 12 and 14 have been cancelled, and thus the rejection as applied to these claims is moot. As discussed below, Applicant believes that the grounds for the rejections would not apply to the newly presented claims. In addition, Applicant does not agree with the Examiner's assertion with regard to alleged lack of guidance in the specification for how to use the claimed mouse to isolate genes encoding antibodies. For the purposes of furthering prosecution only, the new claims do not recite the phrase "or a gene encoding such an antibody." Applicant reserves the right to pursue corresponding claims in a continuation application.

The Examiner indicates that "If the target antigen is not expressed in the context of baculovirus, then using the transgenic of claim 1 is moot because the method can be performed with a wild-type mouse." (Office Action at page 3.) New claim 16 is directed to a method of making antibodies using the transgenic mouse of claim 1, *i.e.*, a transgenic mouse whose genome

comprises a nucleic acid sequence encoding baculovirus gp64, wherein the gp64 is soluble and lacks a transmembrane region, and wherein the mouse is fertile, and an immunogen that includes a baculovirus particle or a portion thereof, wherein the particle or portion thereof comprises gp64 and the target antigen. This was implied in claims 11 and 12 as originally presented. These claims are now cancelled and replaced with new claims 16 and 17, which make the "baculovirus gp64" aspect explicit.

The Examiner has also asserted that: "Since the time of filing, Saitoh (*J. Immunological Methods*, 2007, Vol. 332, pg 104-117) teaches PepT1 must be expressed on the surface of baculoviral particles which is not readily apparent from the teachings in the specification and is considered essential to the invention." (Office Action at page 2-3). The Examiner continues:

The specification does not teach how to use the method to induce antibodies against any target. The specification fails to teach that the target antigen must be a membrane protein that is not from baculovirus and that it must be displayed on the surface of a baculovirus administered to the gp64 transgenic mouse. (Office Action at page 3.) (Emphasis added.)

The Examiner concludes: "Accordingly, the specification is missing essential information for those of skill to use the mice of claim 1 to induce an antibody as claimed. As such, the specification fails to teach those of skill how to use the method as claimed." (Office Action at page 4.) Applicant respectfully disagrees.

The Examiner appears to require that any method of making antibodies in the gp64 transgenic mice of claim 1 be necessarily limited to a target antigen that is both a membrane protein and is displayed on the surface of a baculovirus that is administered to the gp64 transgenic animals. The Examiner further asserts that there is no support in the specification for either of these alleged requirements. Applicant reminds the Examiner that the general problem the inventors set out to solve was to reduce or eliminate the production of antibodies to highly immunogenic background viral antigens that typically contaminate virally-expressed target antigens. To that end, the inventors set out to develop, and did develop, a line of fertile mice that were transgenic for the soluble form of one such background antigen, gp64. As the Applicant

has disclosed, the gp64 transgenic mice had the fertility of wild-type animals (See Example 3) and showed immunologic tolerance to gp64. Thus, the methods of the amended claims allow one of skill in the art to efficiently generate specific antibodies to a desired protein using an immunogen that contains contaminating background antigens, e.g., gp64.

The specification makes clear that the target antigen need not be limited to a membrane protein, but can be, for example "selected from any substance having antigenicity. Specifically, proteins, sugar chains, lipids, inorganic substances, or such are known as substances showing antigenicity." (Specification at page 3, lines 33-36.) It was well known at the time the application was filed that baculoviral expression systems could be used to express and generate antibodies to exogenous non-membrane proteins. Applicant draws the Examiner's attention to Lindley *et al.*, *J. Immunological Methods*, 2000, Vol. 234: 123-135) which has already been submitted in an Information Disclosure Statement and which describes the use of a baculovirus system to make antibodies to the human nuclear receptor proteins LXR β and FXR. Thus, the claimed method can be used to generate antibodies against any target antigen as long as it is administered in the context of a baculovirus particle or portion thereof that includes gp64.

Contrary to the Examiner's assertion, the target antigen need not be displayed on the surface of a baculovirus for one of skill in the art to practice the method of the claims. The specification describes immunogens in many forms and makes clear that the common feature shared by all these forms is not display on a baculoviral surface, but rather the presence of contaminating background antigens:

More specifically, examples of the immunogens of the present invention comprise *cells, cell culture solutions, cell lysates, viruses, and crude antigens*, in which membrane proteins may be contaminating as background antigens.*Whole cells or viruses as well as portions thereof* can be used as the immunogens. Furthermore, just *cell membrane or viral envelope portions* may be used as the immunogens. When such whole cells or viruses, or portions thereof, such as their cell membrane or viral envelope, are used as the immunogen, membrane proteins comprised in the cell membrane or viral envelope contaminate as background antigens. (Specification at page 9, lines 16-19 and lines 20-25.) (Emphasis added.)

Upon reading the Applicant's specification, one of skill in the art would recognize that the method of the claims could be used for any target antigen that was contaminated with background gp64 protein. What is claimed is a method for the efficient production of antibodies to a specific immunogen when that immunogen happens to be contaminated with highly immunogenic gp64 protein. The specification does not, as the Examiner asserts, "fail to teach" that the target antigen "must be a membrane protein and must be displayed on the surface of a baculovirus." Rather, the transgenic mice of the claims have broader utility than the Examiner asserts and there is no reason to limit the scope of the claims to that proposed by the Examiner on pages 4-5 of the Office Action.

As the Applicant understands it, the Examiner has also based his rejection on concerns about the experiment described in Example 4. He states: "While the specification cites Fig. 3 and states mice expressing soluble gp64 induced tolerance (pg 20, lines 17-19), Fig. 3 merely shows expression of soluble gp64. Accordingly, applicant's conclusion based on Fig. 3 is flawed." (Office Action at page 4.) It is unclear why the Examiner believes that Figure 3 "merely shows expression of soluble gp64." Figure 3 is an immunoblot analysis and the methods used are clearly described in paragraphs [0095], [0096] and [0098] of the U.S. published application (US 2008/0040820). Aliquots of budding baculovirus that expressed PepT1 were electrophoresed on an SDS polyacrylamide gel; the electrophoresed proteins were transferred to a PVDF membrane and probed with either sera collected from non-transgenic control animals (lanes #5, #6 and #8 of Figure 3) that had been immunized with a budding baculovirus expressing PepT1 or sera collected from sgp64 transgenic mice (lanes #89, #90 and #91) that had been immunized with a budding baculovirus expressing PepT1. Antibody binding was detected with biotinylated anti-mouse IgG followed by streptavidin alkaline phosphatase. As the specification indicates at paragraph [0099]: "In the case of non-transgenic mice (non-Tgm), staining with anti-mouse IgG resulted in strong staining for all three mice" (See lanes #5, #6 and #8 of Figure 3). In contrast, "[T]here was hardly any gp64 staining for the sgp64Tgm." (Specification at paragraph [0099]; See lanes #89, #90 and #91 of Figure 3.)

Far from supporting a rejection for lack of utility, the immunoblot of Figure 3 demonstrates the usefulness of the sgp64 transgenic mice. Sera from wild-type mice that had been immunized with a budding baculovirus reacted strongly with baculovirus gp64; sera from the sgp64 transgenic animals did not, indicating that the sgp64 transgenic animals were tolerant to gp64. Moreover, the Examiner's contention that "Most importantly, applicants do not obtain antibodies against PepT1" (Office Action at page 4) obscures the point that the Figure makes. The fact that anti-PepT1 antibodies were not assayed in this experiment is largely irrelevant to the major usefulness of this mouse, which is demonstrated in Figure 3.

The Examiner's comments (Office Action at page 4) with respect to the dose of the baculovirus particles and the structure of the antigen that was used in Example 4, which appear to be more relevant to enablement than to utility under 35 U.S.C. §101, are misdirected. The specification is clear as to what was done and the methods can readily be replicated by one of skill in the art.

In view of the above, Applicant submits that the present claims are in condition for allowance, which action is requested.

35 U.S.C. §112, first paragraph

The Examiner has rejected claims 11, 12, and 14 for lack of written description, alleging that because the invention lacks utility, one of skill in the art would not know how to use the claimed invention. Without conceding that the claims as previously presented fail to satisfy this requirement, and solely for the purpose of furthering prosecution, claims 11, 12 and 14 have been cancelled, and thus the rejection as applied to these claims is moot.

Double patenting

The Examiner has made provisional obviousness-type double patenting rejections based on claims 1 and 2 of the co-pending Application No. 10/516603. (Office Action at page 6). The allegedly conflicting claims of co-pending Application No. 10/516603 have not been issued. Because the co-pending Application No. 10/516603 has not issued as a patent and because the

claims in the present application are not otherwise currently allowable, no terminal disclaimer is required for the present application. Upon notification that there is otherwise allowable subject matter in the present application, Applicants will file an appropriate terminal disclaimer if one is needed.

Please charge any required fees and apply any other charges or credits to deposit account 06-1050, referencing attorney docket no. 14875-0167US1.

Respectfully submitted,

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